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Atrial Dilation and Altered Function Are Mediated by Age and Diastolic Function But Not Before the Eighth Decade

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OBJECTIVES This study investigated changes in left atrial (LA) volumes and phasic atrial function, by deciles, with normal aging.

BACKGROUND LA volume increase is a sensitive independent marker for cardiovascular disease and adverse outcomes. To use this variable more effectively as a marker of pathology and a gauge of outcome, physiological changes due to aging alone need to be quantitated.

METHODS A detailed transthoracic echocardiogram was performed in 220 normal subjects; 89 (41%) were male and their age ranged from 20 to 80 years (mean 45 ± 17 years). Maximum (end-ventricular systole), minimum (end-ventricular diastole), and pre–a-wave volumes were measured using the biplane method of disks. LA filling, passive emptying, conduit and active emptying volumes, and fractions were calculated. Transmitral inflow, pulmonary vein flow, and pulsed-wave Doppler tissue imaging parameters were measured as expressions of left ventricular diastolic function. For purposes of analysis, subjects were divided by age deciles.

RESULTS LA indexed maximum (0.05 ml/m^2 per year) and minimum (0.06 ml/m^2 per year) volume increased with age but only became significant in the eighth decade (26.0 ± 6.3 ml/m^2, $p = 0.02$, and 13.5 ± 3.9 ml/m^2, respectively; $p < 0.001$). Impaired left ventricular diastolic relaxation was apparent in decade 6 and was associated with a shift in phasic LA volumes so that LA expansion index and passive emptying decreased with increasing age, whereas active emptying volume increased.

CONCLUSIONS In normal healthy subjects, LA indexed volumes remain nearly stable until the eighth decade when they increase significantly. Therefore, an increase in LA size that occurs before the eighth decade is likely to represent a pathological change. Changes in phasic atrial volumes develop earlier consequent to age-related alteration in LV diastolic relaxation. (J Am Coll Cardiol Img 2011;4: 234–42) © 2011 by the American College of Cardiology Foundation

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Enlargement of the left atrium has been used as a marker for left ventricular (LV) dysfunction (1) and is an independent predictor of major cardiovascular outcomes (2,3). An increase in left atrial (LA) size incrementally increases the risk of the development of atrial fibrillation (4,5), the incidence of which increases with age (6–8).

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It has been assumed that normal aging exerts changes that increase atrial size and impair atrial function, thereby resulting in the observed proportional age-related increase in atrial fibrillation. There are conflicting reports in the literature in relation to age-related changes in LA size; some demonstrate no change (9) and others an increase (10–12). A detailed analysis of the changes in LA size and phasic function with each decade of increasing age has not previously been reported in a large healthy cohort. Knowledge of the contribution of aging to atrial enlargement is essential for segregating pathological from physiological alterations.

Thus, the aims of this study were to determine changes in LA volumes and phasic atrial function with normal aging. We hypothesized that with normal aging: 1) LA volume is unchanged until advanced age; 2) passive atrial emptying is progressively decreased in parallel with impaired left ventricular (LV) relaxation; 3) active atrial emptying is progressively increased in parallel with impaired LV relaxation; and 4) the LA expansion index is decreased due to decreased LA compliance with normal aging.

METHODS

Study approval was obtained from the Committees for Human Research at Westmead and Liverpool Hospitals in Sydney, Australia, for recruitment and collection of data from healthy individuals. All subjects provided written informed consent before enrollment. Two hundred and twenty healthy volunteers were enrolled from the community through an advertising campaign involving presentations and posters. Subjects were screened by a detailed medical history and had to be free of any known cardiovascular disease or cardiovascular risk factors. Eighty-nine subjects (41%) were male, and ages ranged from 20 to 80 years with a mean of 45 ± 17 years. In addition to transthoracic echocardiography, all subjects underwent a detailed clinical evaluation including cardiovascular symptoms and history, medication history, family history, height, weight, blood pressure monitoring, electrocardiography, and normal blood tests to exclude any underlying pathology. Furthermore, all subjects were required to have normal findings on echocardiographic examinations, particular with reference to LV hypertrophy, regional and global LV function, and valvular abnormalities. Subjects were excluded if there was any indication of ischemic heart disease, significant valvular disease, peripheral vascular or cerebrovascular disease, hypertension or diabetes, or were on any cardioactive medications. Thus, despite the inherent limitations in selecting truly "normal" subjects, we have made every attempt in the current cohort to accurately represent a normal, healthy aging population.

Subject groups. The normal subjects (n = 220) were divided into groups based on decades of life; decade 3 (n = 51), decade 4 (n = 48), decade 5 (n = 30), decade 6 (n = 41), decade 7 (n = 31), and decade 8 (n = 19). Chronological aging was determined as years since birth. Advanced age was defined as ≥70 years and older in the current cohort.

Echocardiography. Standard transthoracic echocardiography was performed according to established laboratory practice using commercially available ultrasound systems (Vivid 5 and 7 systems, General Electric, Horten, Norway). Measurements were performed offline using Echopac PC 6.1.0. (GE-Vingmed, Horten, Norway) (9).

LV and LA measurements. LV volumes were measured using the modified Simpson's biplane method of disks, and LV systolic function was determined by calculation of LV ejection fraction (13). LV mass index was also determined using the area-length method (14).

LA maximum volume (just before mitral valve opening), LA minimal volume (at mitral valve closure), and LA pre–a-wave volume (onset of P-wave on electrocardiography) were measured using the biplane method of disks (14). Phasic LA volumes and fractions were calculated as follows (9):

- LA total emptying volume = LA maximum volume − LA minimum volume
- LA total emptying fraction = LA total emptying volume/LA maximum volume
- Expansion index = LA filling volume/LA minimum volume
- Passive emptying volume = LA maximum volume − LA pre–a-wave volume

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
LA = left atrial
LV = left ventricular

- Passive emptying fraction = Passive emptying volume/LA maximum volume
- Conduit volume = LV stroke volume − (LA total emptying volume)
- Active emptying volume = LA pre–a-wave volume − LA minimum volume
- Active emptying fraction = Active emptying volume/LA pre–a-wave volume

All volumes were indexed to body surface area and allometric height (height$^{2.7}$) (15).

Doppler parameters. Transmitral inflow velocity by pulsed-wave Doppler imaging was obtained with the sample volume placed at the tips of the mitral leaflets. Peak velocity in early diastole (E-wave during early LV relaxation) and late diastole (A-wave during atrial contraction) were measured and the E/A ratio calculated. The velocity time integral of the A-wave was measured and the atrial emptying fraction estimated as the A-wave velocity time integral divided by the total mitral inflow velocity time integral. Additionally, the deceleration time and A-wave duration were measured (9).

Atrial ejection force was calculated from the following equation: atrial ejection force = 0.5 × ρ (density of blood = 1.06 g/cm^3) × mitral orifice area × (peak A velocity)^2, as previously described (16).

Pulmonary vein velocities were obtained by pulsed-wave Doppler examination from the apical 4-chamber view by placing the sample within the proximal 2 cm of the right upper pulmonary vein. Peak systolic, diastolic, and atrial reversal velocities were measured and the peak systolic–to–peak diastolic velocity ratio obtained. The systolic fraction was calculated as the systolic velocity time integral divided by the total forward pulmonary vein flow velocity time integral. The difference between the atrial reversal duration and the mitral A-wave duration were calculated.

Pulsed-wave Doppler tissue imaging was used to measure peak velocity in systole (S′), early diastole (E′), and late diastole (A′), with the sample volume placed at the septal and lateral annulus (17). The average of the 2 segments were calculated. The E/E′ ratio was calculated as a measure of LV end-diastolic pressure.

LV diastolic dysfunction was classified according to previously defined standard criteria (18,19) as normal (deceleration time = 160 to 240 ms, E/A ratio = 0.9 to 1.5, E′ velocity ≥10 cm/s), mild (deceleration time >240 ms, E/A ratio <0.9, E′ velocity <10 cm/s), moderate (deceleration time = 160 to 240 ms, E/A ratio = 0.9 to 1.5, E′ velocity <8 cm/s), and severe (deceleration time <160 ms, E/A ratio >2.0, E′ velocity <5 cm/s). If diastolic function was undetermined using these criteria, E/E′ ratio and pulmonary vein flow were additionally used for classification (18).

Variability. Ten studies were randomly selected for interobserver and intraobserver variability. LA volumes were remeasured by the same observer and by a second independent observer from the digital data using an offline system. Interstudy variability was performed on 10 subjects by repeating their imaging approximately 1 h after initial images were obtained.

Analysis. All values are expressed as a mean ± SD. Differences among the decades were examined by 1-way analysis of variance with Bonferroni post hoc analysis. Stepwise linear regression analysis using body surface area, body mass index, and allometric height were performed to determine independent predictors of LA volumes. Linear regression analysis was performed to investigate the correlation of age with LA volume and function parameters, after adjusting for effects of sex. Nonparametric chi-square analysis was used to examine differences in categorical variables (sex and diastolic function grade) among the decades. The differences between grades of diastolic function with demographic and echocardiographic parameters were examined by unpaired Student *t* test analysis. Bland-Altman (20) analysis was performed to measure interobserver and intraobserver and interstudy variability. Data were considered significant if $p < 0.05$. Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The mean values for demographic and echocardiographic LV variables by decades are listed in Table 1. There were no significant differences in sex ($p = 0.50$), body surface area ($p = 0.11$), allometric height ($p = 0.08$), and heart rate ($p = 0.74$) among the decades. All patients were normotensive, although mean arterial blood pressures were significantly higher in subjects over decade 5. LV echocardiographic parameters were similar for all decades (Table 1).

LA volumes. The mean values for LA indexed volumes by decades are listed in Table 2. LA maximum and minimum volumes increased significantly only in decade 8 ($p = 0.02$ and $p < 0.001$, respectively), whereas pre–a-wave volume increased in decade 7 ($p < 0.001$). LA expansion index decreased in decade 8 ($p < 0.001$), whereas in the

Table 1. Mean Values for Demographic and LV Indexed Parameters Among Decades of Life

	Decade 3 (n = 51)	Decade 4 (n = 48)	Decade 5 (n = 30)	Decade 6 (n = 41)	Decade 7 (n = 31)	Decade 8 (n = 19)
Age, yrs	25 ± 3	35 ± 3	45 ± 3	54 ± 3	65 ± 3	75 ± 4
Sex, % male	37	48	50	37	29	42
Height, cm	168 ± 10	170 ± 10	171 ± 10	167 ± 8	163 ± 10	165 ± 15
Allometric height, $m^{2.7}$	4.1 ± 0.7	4.2 ± 0.6	4.3 ± 0.6	4.0 ± 0.5	3.8 ± 0.6	3.9 ± 1.0
Weight, kg	67 ± 13	77 ± 16	73 ± 14	73 ± 16	71 ± 18	73 ± 14
Body mass index, kg/m^2	23.6 ± 3.7	26.7 ± 4.9*	24.9 ± 3.7	26.2 ± 4.9	26.5 ± 5.0	26.9 ± 4.0
Body surface area, m^2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2
Systolic blood pressure, mm Hg	114 ± 11	115 ± 10	119 ± 12	121 ± 10	124 ± 12*†	128 ± 13*†
Diastolic blood pressure, mm Hg	68 ± 8	73 ± 8	75 ± 8*	77 ± 8*	73 ± 9	76 ± 9*
Mean arterial pressure, mm Hg	84 ± 7	87 ± 8	90 ± 8*	91 ± 8*	90 ± 8*	93 ± 10*
Heart rate, beats/min	71 ± 11	69 ± 12	70 ± 11	67 ± 11	69 ± 12	71 ± 11
LV end-diastolic volume indexed, ml/m^2	53.9 ± 9.4	48.1 ± 10.1	50.6 ± 12.1	48.3 ± 8.4	49.7 ± 10.0	49.2 ± 9.1
LV end-systolic volume indexed, ml/m^2	21.7 ± 4.4	19.0 ± 4.6	20.3 ± 5.7	19.0 ± 4.5	19.5 ± 5.3	19.0 ± 5.1
LV ejection fraction, %	60 ± 4	61 ± 4	60 ± 4	60 ± 5	61 ± 5	61 ± 6
LV mass indexed, g/m^2	72 ± 19	64 ± 21	68 ± 21	76 ± 22	64 ± 13	68 ± 16

*$p < 0.05$ compared with decade 3. †$p < 0.05$ compared with decade 4.
LV = left ventricular.

seventh decade, passive emptying decreased ($p < 0.001$) with a reciprocal increase in active emptying ($p < 0.001$) (Figs. 1 and 2).

Linear regression analysis was performed to determine independent predictors of LA volume using body size measurements (body surface area, body mass index, and allometric height). Body surface area was the only measurement that independently predicted LA maximum ($R^2 = 0.13$, $p < 0.001$), minimum ($R^2 = 0.11$, $p < 0.001$) and pre–a-wave volumes ($R^2 = 0.10$, $p < 0.001$). Subsequent indexing of volumes to body surface area was used as the standard for all analysis.

There were no significant effects of sex on indexed LA maximum ($p = 0.52$), minimum ($p = 0.41$), pre–a-wave ($p = 0.44$), total emptying ($p = 0.84$), and conduit ($p = 0.13$), passive ($p = 0.93$), and active emptying ($p = 0.81$) volumes.

There were significant positive linear correlations (Table 3) between age and indexed LA maximum (B coefficient 0.05 ml/m^2, SE = 0.02), minimum (B coefficient 0.06 ml/m^2, SE = 0.01), and active emptying (B coefficient 0.05 ml/m^2, SE = 0.01) volumes. LA maximum volume did not correlate with LV mass ($R^2 = 0.01$, $p = 0.18$); however, none of the enrolled subjects had LV hypertrophy. Significant negative linear correlations were present between age and LA total emptying fraction (B coefficient = −0.004 ml/m^2, SE = 0.01) and expansion index (B coefficient = −0.69 %, SE =

Table 2. Mean Values for LA Volumes and Phasic Volumes Indexed to Body Surface Area Among Decades of Life

	Decade 3 (n = 51)	Decade 4 (n = 48)	Decade 5 (n = 30)	Decade 6 (n = 41)	Decade 7 (n = 31)	Decade 8 (n = 19)
LA maximum volume indexed, ml/m^2	22.1 ± 5.2	21.4 ± 3.3	23.4 ± 5.0	22.7 ± 4.5	23.0 ± 5.1	26.0 ± 6.3*†
LA minimum volume indexed, ml/m^2	9.1 ± 2.7	9.2 ± 2.1	9.7 ± 2.9	9.3 ± 2.3	10.7 ± 3.0	13.5 ± 3.9*†‡§‖
Pre–a-wave volume indexed, ml/m^2	13.2 ± 4.1	13.3 ± 2.6	14.6 ± 4.2	14.6 ± 3.0	16.4 ± 3.5*†	19.9 ± 5.6*†‡§‖
LA total emptying volume indexed, ml/m^2	12.9 ± 3.4	12.2 ± 2.6	13.7 ± 3.4	13.4 ± 3.9	12.3 ± 3.0	12.5 ± 3.6
LA total emptying fraction, %	59 ± 7	57 ± 8	59 ± 8	59 ± 10	53 ± 7	48 ± 7*†‡§
LA expansion index, %	149 ± 43	139 ± 43	150 ± 47	152 ± 55	120 ± 35	96 ± 26*†‡§
Conduit volume indexed, ml/m^2	19.2 ± 5.8	16.9 ± 6.7	16.6 ± 6.1	15.8 ± 4.9	17.9 ± 6.1	17.7 ± 6.8
Passive emptying volume indexed, ml/m^2	8.9 ± 2.8	8.1 ± 1.8	8.8 ± 2.7	8.2 ± 3.2	6.6 ± 2.8*‡	6.0 ± 2.4*‡
Passive emptying fraction, %	40.6 ± 9.7	38.1 ± 6.3	37.9 ± 9.3	35.1 ± 10.8	27.9 ± 7.6*†‡§	23.3 ± 8.4*†‡§
Active emptying volume indexed, ml/m^2	4.0 ± 1.8	4.0 ± 1.4	4.9 ± 1.9	5.3 ± 1.9	5.7 ± 1.2*†	6.5 ± 2.2*†‡
Active emptying fraction, %	30.2 ± 8.4	30.4 ± 8.8	33.3 ± 7.7	35.1 ± 8.5*†	35.1 ± 7.2*†	32.8 ± 5.3

*$p < 0.05$ compared with decade 3. †$p < 0.05$ compared with decade 4. ‡$p < 0.05$ compared with decade 5. §$p < 0.05$ compared with decade 6. ‖$p < 0.05$ compared with decade 7.
LA = left atrial.

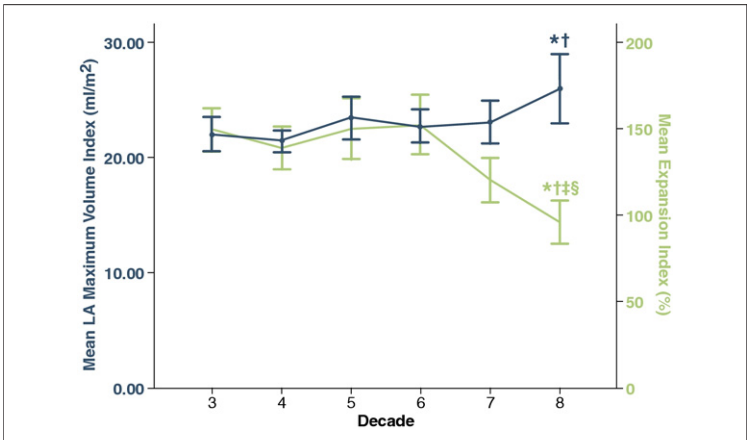

Figure 1. Changes With Decade for LA Maximum Volume Indexed and LA Expansion Index

LA maximum volume **(blue line)** significantly increased whilst LA expansion index **(green line)** decreased only in decade 8. Error bars indicate 95% confidence interval. *p < 0.05 compared with decade 3. †p < 0.05 compared with decade 4. ‡p < 0.05 compared with decade 5. §p < 0.05 compared with decade 6. LA = left atrial.

0.19). Age also correlated inversely with passive emptying volume (B coefficient = −0.05 ml/m^2, SE = 0.11).

Diastolic function. The mean values for transmitral inflow and pulmonary vein flow parameters by decade are listed in Table 4. E/A ratio and E′ velocity decreased, whereas atrial fraction and systolic fraction increased as early as decade 4. Changes in peak E velocity were observed in decade 6.

LV diastolic function across the decades is listed in Table 4. The incidence of mild diastolic dysfunction was significant from decade 6; 86% of the subjects had normal diastolic function, and the remaining 14% had only mild diastolic dysfunction. There was no association between diastolic function and sex (p = 0.85). Subjects with mild diastolic dysfunction were significantly older (p < 0.001; 67 ± 9 years vs. 42 ± 15 years), with a higher mean arterial blood pressure (p = 0.03, 91 ± 8 mm Hg vs. 88 ± 8 mm Hg) and heart rate (p = 0.005; 74 ± 11 beats/min vs. 68 ± 11 beats/min). LA maximum (p = 0.29) and minimum (p = 0.07) volumes did not differ between the subjects with mild diastolic dysfunction and normal diastolic function. Mild diastolic dysfunction was associated with increased active emptying volume (p < 0.001) and fraction (p = 0.005) and atrial ejection force (p < 0.001). Conversely passive emptying volume (p < 0.001) and fraction (p < 0.001) were reduced with mild diastolic dysfunction.

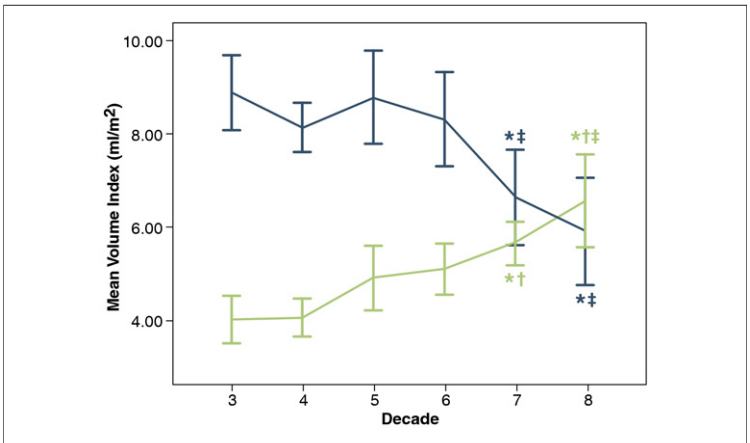

Figure 2. Changes With Decade for Passive Emptying Volume Indexed and Active Emptying Volume Indexed

Passive emptying volume **(blue line)** decreased whilst active emptying volume **(green line)** increased significantly in decade 7. Error bars indicate 95% confidence interval. *p < 0.05 compared with decade 3. †p < 0.05 compared with decade 4. ‡p < 0.05 compared with decade 5.

Variability. Bland-Altman analysis for LA maximum volume demonstrated an intraobserver mean difference of −0.3 ml/m^2 (95% confidence interval [CI]: −2.8 to 2.4 ml/m^2), an interobserver mean difference of −0.2 ml/m^2 (95% CI: −2.8 to 2.4 ml/m^2), and an interstudy mean difference of −0.9 ml/m^2 (95% CI: −3.8 to 2.0 ml/m^2), demonstrating excellent reproducibility. Bland-Altman analysis for LA minimum volume demonstrated an intraobserver mean difference of −0.3 ml/m^2 (95% CI: −2.0 to 1.6 ml/m^2), an interobserver mean difference of −0.2 ml/m^2 (95% CI: −2.0 to 1.6 ml/m^2), and an interstudy mean difference of −1.8 ml/m^2 (95% CI: −4.3 to 0.7 ml/m^2). Bland-Altman analysis for LA pre–a-wave volume demonstrated an intraobserver mean difference of 0.1 ml/m^2 (95% CI: −1.5 to 1.6 ml/m^2), an interobserver mean difference of 0.1 ml/m^2 (95% CI: −1.5 to 1.6 ml/m^2), and an interstudy mean difference of 0.6 ml/m^2 (95% CI: −1.4 to 2.6 ml/m^2).

DISCUSSION

LA size is increasingly used as a marker for cardiovascular disease (1,4,5); therefore, enlargement and changes in atrial function due to aging need to be carefully quantitated to differentiate physiological from pathological changes. No study has previously examined LA changes and age-related LV diastolic dysfunction, categorized by decades of life in a large group of healthy individuals.

Table 3. Linear Regression, After Adjusting for Sex, Between Age and LA Volume and Function Parameters

	R^2	p Value
LA maximum volume indexed, ml/m^2	0.06	0.01*
LA minimum volume indexed, ml/m^2	0.11	<0.001*
LA total emptying volume indexed, ml/m^2	0.04	0.65
LA total emptying fraction, %	0.08	<0.001*
LA expansion index, %	0.06	<0.001*
Conduit volume indexed, ml/m^2	0.05	0.24
Passive emptying volume indexed, ml/m^2	0.12	<0.001*
Passive emptying fraction, %	0.26	<0.001*
Active emptying volume indexed, ml/m^2	0.19	<0.001*
Active emptying fraction, %	0.05	0.02*

*p < 0.05.

The salient finding of this study is that significant increases in LA volume occur only in the eighth decade with healthy aging. This observation confirms similar findings observed in a smaller group (12) and also in a large cross-sectional sample (n = 1,012) of middle-aged to elderly healthy subjects recruited from the community (21). The unique feature of our study is that it included adults of all ages and examined the temporal relationship between diastolic changes and changes in LA volumes. Therefore, an increase in LA size in all but the oldest normal subjects (free of atrial arrhythmias, diastolic dysfunction, and valvular disease) should be considered an indicator of underlying cardiovascular pathology. LA minimum volume, a correlate of LV filling pressure (22), also demonstrated an increase only at advanced age, similar to maximal LA volume. Indexed LA volumes were not altered by sex, as demonstrated previously (10). In this healthy cohort, no significant differences were observed between LA volumes indexed to either body surface area or to allometric height, as has also been recently described in an elderly population (23,24), whereas only body surface area was an independent predictor of LA size.

We observed that diastolic changes occurred in the sixth decade resulting in mild grade diastolic dysfunction. Klein et al. (25) also demonstrated significantly altered LV filling dynamics in subjects

Table 4. Mean Values for Mitral Inflow, Pulmonary Vein Flow, Tissue Doppler Imaging, and Diastolic Function Among Decades of Life

	Decade 3 (n = 51)	Decade 4 (n = 48)	Decade 5 (n = 30)	Decade 6 (n = 41)	Decade 7 (n = 31)	Decade 8 (n = 19)
Mitral inflow						
E velocity, m/s	0.84 ± 0.16	0.78 ± 0.11	0.75 ± 0.17	0.71 ± 0.14*	0.65 ± 0.15*†	0.65 ± 0.17*†
A velocity, m/s	0.49 ± 0.14	0.54 ± 0.13	0.61 ± 0.21*	0.64 ± 0.16*	0.72 ± 0.15*†	0.79 ± 0.27*†‡§
E/A ratio	1.8 ± 0.5	1.5 ± 0.4*	1.3 ± 0.3*	1.2 ± 0.3*†	0.9 ± 0.2*†‡	0.9 ± 0.2*†‡§
A duration, ms	179 ± 53	176 ± 32	199 ± 47	210 ± 52*†	195 ± 41	177 ± 29
Deceleration time, ms	193 ± 32	200 ± 36	200 ± 35	208 ± 33	212 ± 46	231 ± 61*†
Atrial fraction, %	27.9 ± 6.2	33.8 ± 7.8*	35.5 ± 6.4*	40.0 ± 8.6*†	45.9 ± 8.3*†‡§	43.3 ± 5.6*†‡
Atrial ejection force, kdynes/m^2	9.6 ± 6.8	12.0 ± 7.2	16.0 ± 14.7	15.6 ± 8.6	20.6 ± 10.7*†	27.8 ± 16.7*†‡§
Pulmonary vein flow						
Systolic velocity, m/s	0.48 ± 0.09	0.53 ± 0.10	0.51 ± 0.08	0.54 ± 0.08*	0.54 ± 0.11	0.53 ± 0.14
Systolic velocity time integral, cm/s	12.2 ± 3.3	13.8 ± 3.4	14.1 ± 2.9	14.9 ± 2.9*	14.7 ± 3.3*	15.1 ± 4.0*
Systolic fraction, %	47.5 ± 9.5	53.1 ± 8.6*	58.5 ± 7.4*	58.1 ± 8.8*	57.7 ± 8.8*	62.4 ± 8.9*†
Diastolic velocity, m/s	0.61 ± 0.12	0.53 ± 0.12*	0.46 ± 0.08*	0.47 ± 0.10*	0.46 ± 0.14*	0.39 ± 0.12*†
Diastolic velocity time integral, cm/s	13.1 ± 3.1	11.9 ± 3.2	10.6 ± 1.8*	10.7 ± 2.8*	10.4 ± 2.9*	9.3 ± 3.4*†
Systolic/diastolic ratio	0.8 ± 0.2	1.0 ± 0.2*	1.1 ± 0.2*	1.3 ± 0.5*†	1.2 ± 0.4*	1.4 ± 0.4*†
Atrial reversal velocity, cm/s	0.25 ± 0.05	0.25 ± 0.06	0.23 ± 0.04	0.28 ± 0.06‡	0.30 ± 0.06*†‡	0.29 ± 0.06‡
Atrial reversal velocity time integral, cm/s	2.7 ± 1.0	2.7 ± 0.9	2.4 ± 0.9	3.1 ± 1.2‡	2.9 ± 0.5	3.1 ± 0.8
Atrial reversal duration, ms	139 ± 51	138 ± 47	145 ± 50	158 ± 56	133 ± 30	142 ± 27
Atrial reversal duration–A duration, ms	−335 ± 72	−345 ± 61	−355 ± 51	−352 ± 56	−362 ± 38	−35 ± 32
Tissue Doppler imaging						
$S'_{average}$ velocity, cm/s	8.9 ± 1.5	8.6 ± 1.6	8.3 ± 1.5	7.9 ± 1.7	7.3 ± 1.5*†	7.4 ± 1.1*
$E'_{average}$ velocity, cm/s	13.8 ± 2.9	11.7 ± 2.9*	10.6 ± 2.3*	8.8 ± 1.9*†‡	7.1 ± 1.7*†‡§	7.0 ± 1.5*†‡§
$A'_{average}$ velocity, cm/s	7.8 ± 1.2	8.8 ± 1.7*	9.3 ± 1.4*	10.0 ± 1.9*†	10.3 ± 1.8*†	11.1 ± 1.8*†‡
$E/E'_{average}$ ratio	6.3 ± 2.3	7.1 ± 2.1	7.4 ± 2.8	8.5 ± 2.5*	9.6 ± 2.8*†‡	9.7 ± 3.4*†‡
Normal, %	100	100	97	85*†	58*†‡§	42*†‡§‖
Mild dysfunction, %	—	—	3	15	42	58

*p < 0.05 compared with decade 3. †p < 0.05 compared with decade 4. ‡p < 0.05 compared with decade 5. §p < 0.05 compared with decade 6. ‖p < 0.05 compared with decade 7.

older than 50 years of age. Normal aging results in myocardial fibrosis, altered collagen properties, and abnormal calcium handling within the myocytes of the left ventricle (26,27). These ultrastructural changes likely result in reduced LV compliance and relaxation (28). This suggests that changes within the myocytes may occur earlier than chronologically advanced age. Therefore, physiological changes may occur before and are likely present for a significant period before manifestation as chronologically advanced age.

Interestingly, normal aging only results in a mild degree of diastolic impairment and the occurrence of worsening grades of dysfunction (e.g., pseudonormal or restrictive filling) may be due to coexistent pathology. Furthermore, this age-related mild diastolic dysfunction was not associated with immediate LA enlargement (29,30), which developed almost 2 decades later. This observation would support the concept that LA volume is a marker of the chronicity of LV diastolic changes, whereas transmitral Doppler imaging–derived LV diastolic measurements are more markers of the LA-to-LV pressure gradient at a time point (1,31–34).

Altered LV relaxation with reduced LV suction results in reduced passive atrial emptying, as previously described (9–11). Consequently, LA active emptying is augmented to compensate for the decreased volume transfer during early diastole (35,36). The reciprocal increase in active atrial emptying leads to augmentation of early LA relaxation (37,38), which is additionally reflected in the increased pulmonary venous systolic fraction with aging (39,40). Thus, it would appear reasonable to surmise that changes in LA phasic function occur largely as an adaptation to LV diastolic changes.

These LA compensatory mechanisms are effective for the sixth and seventh decades, but subsequently a plateau in active emptying fraction is observed in the eighth decade. This is accompanied by a decline in LA compliance, observed as a reduction in the LA expansion index in the eighth decade. The causes for reduced atrial compliance could be multifactorial. An increase in interstitial atrial fibrosis as part of the normal aging process (41–43), similar to that observed in the LV, may contribute to LA noncompliance. Additionally, the observed LA changes may in part be consequent to age-related LV diastolic dysfunction.

Altered LA compliance prevents further compensatory augmentation of active atrial emptying. Subsequently, atrial enlargement occurs when the LA stroke volume has to increase beyond that of the Frank-Starling relationship. Therefore, atrial enlargement likely occurs as a consequence of long-term adaptation to LV diastolic dysfunction and reduced atrial compliance, as a consequence of interstitial fibrosis at advanced age in healthy individuals.

Study limitations. The present study was performed with relatively small numbers of subjects, and the subset analysis by decades may lead to beta errors. However, similar changes in LA size at the extremes of age have previously been reported (12,21).

It was beyond the scope of the current study to perform exercise stress tests to confirm normal cardiovascular reserve and exclude underlying ischemia in 220 subjects. However, we made every attempt in line with what would be considered acceptable clinical practice to ensure that the current cohort accurately represents a normal, healthy aging population.

Correlation with histopathology would have permitted a better understanding of the underlying pathophysiological mechanisms, but it was considered impractical to obtain biopsy specimens from healthy normal individuals.

The biological age score has been suggested to be superior to chronological age in assessing cardiovascular variables in healthy aging (44). However, derivation of a similar biological score was beyond the scope of our study.

CONCLUSIONS

Normal healthy aging does not significantly alter indexed LA maximum or minimum volumes until the eighth decade of life. However, changes in phasic LA function occurred as early as decade 6 as a compensatory response to age-related LV diastolic dysfunction. At advanced age, long-term adaptation to LV diastolic dysfunction together with reduced LA compliance results in atrial enlargement.

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